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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference OREZ/P29765PC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/IB 03/03163	International filing date (day/month/year) 18.06.2003 ✓	Priority date (day/month/year) 18.06.2002 ✓
International Patent Classification (IPC) or both national classification and IPC C07K14/705		
Applicant CEPEP AB et al. ✓		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet. ✓
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:
- I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☒ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 14.01.2004 ✓	Date of completion of this report 20.01.2005
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Gunster, M Telephone No. +31 70 340-4412 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/IB 03/03163**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-92 as originally filed

Claims, Numbers

1-76 as originally filed

Drawings, Sheets

1/44-44/44 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
☒ filed together with the international application in computer readable form.
☒ furnished subsequently to this Authority in written form.
☒ furnished subsequently to this Authority in computer readable form.
☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

- ☐ restricted the claims.
☐ paid additional fees.
☐ paid additional fees under protest.
☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
☒ the parts relating to claims Nos. 54 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	54
	No: Claims	
Inventive step (IS)	Yes: Claims	54
	No: Claims	
Industrial applicability (IA)	Yes: Claims	54
	No: Claims	

2. Citations and explanations

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see separate sheet

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Re Item IV

Lack of unity of invention

The application as filed is considered to lack unity of invention since its subject-matter relates not to one, but rather to 31933 separate inventions not linked together by a common underlying inventive concept as required by Rules 13.1 and 13.2 PCT.

The claims and the inventions to which the 31933 separate inventions relate may be grouped together as follows:

Invention 1: claims 1-16 [completely]

Invention 2: claims 17-27, 29, 31, 33, 35, 37, 39, 41-44, 47-53, 61-76 [partially]

” ” ” ”

Invention 31923: claims 17-27, 29, 31, 33, 35, 37, 39, 41-44, 47-53, 61-76 [partially]

Invention 31924: claims 17-21, 42-44, 47-52, 61-76 [partially], 28 [completely]

Invention 31925: claims 17-21, 42-44, 47-52, 61-76 [partially], 30 [completely]

Invention 31926: claims 17-21, 42-44, 47-52, 61-76 [partially], 32 [completely]

Invention 31927: claims 17-21, 42-44, 47-52, 61-76 [partially], 34 [completely]

Invention 31928: claims 17-21, 42-44, 47-52, 61-76 [partially], 36 [completely]

Invention 31929: claims 17-21, 42-44, 47-52, 61-76 [partially], 38 [completely]

Invention 31930: claims 17-21, 42-44, 47-52, 61-76 [partially], 40 [completely]

Invention 31931: claims 17-21, 42-44, 47-52, 61-76 [partially], 45, 46 [completely]

Invention 31932: claim 54 [completely]

Invention 31933: claims 55-60 [completely]

According to Rule 13.2 PCT, an international patent application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features. Special technical features are such features that define the contribution of the claimed invention over the prior art.

The contributions claimed in the present application which are allegedly made over the prior art are:

- a) Methods for identifying, designing, making and checking for cell penetrating peptides using the "Z" formula.
- b) The cell penetrating peptide of SEQ ID 1, and its various uses.

” ” ” ” ”

**INTERNATIONAL PRELIMINARY
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- p) The cell penetrating peptide of SEQ ID 31922, and its various uses.
- q) The cell penetrating peptide being derived from a transcription factor, and its various uses.
- r) The cell penetrating peptide being derived from a secretase, and its various uses.
- s) The cell penetrating peptide being derived from a GLP-1 receptor, and its various uses.
- t) The cell penetrating peptide being derived from a CGRP receptor, and its various uses.
- u) The cell penetrating peptide being derived from a AT2 type receptor, and its various uses.
- v) The cell penetrating peptide being derived from PrpC, and its various uses.
- w) The cell penetrating peptide being derived from APP or PS-1, and its various uses.
- x) The cell penetrating peptide comprising the amino acid sequence IVIAKLKA, and its various uses.
- y) A cell-selective delivery system comprising a cell penetrating peptide with a cell-selective protease cleavage site and a cytostatic or cytotoxic agent.
- z) A vector for transfecting a cell, the vector comprising a nucleic acid component, a polycation conjugate and a cell-penetrating peptide.

These contributions are not so linked to form a single general inventive concept in the sense of Rules 13.1 and 13.2 PCT. The reasons therefor are the following:

The identified 31933 inventions involve the common concept of "being identifiable by the method of claim 1 (i.e. they fit the "Z" formula)" as the sole common link. However, this concept does not define a contribution over the prior art. Cell penetrating peptides that are identifiable by the method of claim 1 and fit the "Z" formula such as penetratin and transportan are known (see for table 1B of the present application and table 2 of LINDGREN ET AL, TIPS (2000) Vol. 21, pages 99-103). Thus the common concept linking the alleged inventions is not new. Therefore, there is no single general inventive concept that links the claimed inventions, which and 13.2 PCT.

The applicant has chosen not to pay additional fees for any additional inventions. Consequently, the present International Preliminary Examination Report (IPER) will be draw up with regards to the main invention only. Said main invention being, in the opinion of the applicant and the International Preliminary Examination Authority, invention 31932. Thus, only claim 54 will be the subject of the present IPER.

Re Item V

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NOVELTY

The subject-matter of claim 54 is new in the sense of Article 33(2) PCT because a cell selective delivery system comprising:

- a) a cell-penetrating peptide comprising a protease consensus site for a protease specifically over expressed by a target cells and
- b) a cytostatic or cytotoxic agent,

wherein said cell-selective delivery system additionally comprises an inactivation sequence repressing the activity of said cell-penetrating peptide, and which is cleaved by said protease is not known in the prior art.

INVENTIVE STEP

The present application meets the requirements of Article 33(1) PCT, because the subject-matter of claim 54 involves an inventive step in the sense of Article 33(3) PCT.

WO0034308 is the **closest prior art** (claims 1-6). This document discloses a cell selective delivery system comprising:

- a) a cell-penetrating peptide comprising a protease consensus site for a protease specifically overexpressed by a target cells and
- b) a cytostatic or cytotoxic agent.

The **additional technical feature** of claim 54 over WO0034308 is that said cell-selective delivery system additionally comprises an inactivation sequence repressing the activity of said cell-penetrating peptide, and which is cleaved by said protease.

The **problem** to be solved by the present invention may therefore be regarded as the provision of an alternative cell delivery system.

The **solution** to this problem can be found in incorporating an inactivation sequence repressing the activity of said cell-penetrating peptide, and which is cleaved by said protease into the cell-selective delivery system of WO0034308.

There is nothing in the prior art that teaches or suggests the skilled person to solve the problem posed in the way presented in claim 54.

Thus, the subject-matter of claim 54 is not obvious for a person skilled in the art.

Therefore the subject-matter of claim 54 involves an inventive step in the sense of

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Article 33(3) PCT.

INDUSTRIAL APPLICATION

The subject-matter of claim 54 is industrially applicable in the field of molecular biology.